REMARKS

Entry of the above amendments and consideration of the following remarks are respectfully requested. Upon entry of the above amendments, this application will contain claims 1-18 and 20-26 pending and under consideration.

In the Office Action dated September 11, 2003, the previous rejections were withdrawn and new rejections were raised. Claims 1-18 and 20-24 were rejected under 35 USC §112. Claims 1-6, 7-11, 13-18, and 20-24 were rejected under 35 USC §103 over Walker et al. (EP 0 500 224) in view of Walker et al. (US 5,470,723). As more fully discussed below, Applicants believe that the claimed invention is patentably distinct from the cited references and respectfully request reconsideration leading to withdrawal of all outstanding rejections and allowance of this application in a timely fashion.

Rejections under 35 USC §112

Independent claims 1 and 20 were rejected as indefinite for reciting the term "possible". Claims 1 and 20 have both been amended by canceling the phrase "said enzyme (d) possibly being provided by enzyme (c) in the case where the latter also has the required exonuclease activity". Claims 1 and 20 now recite that the method includes treating the sequences with an enzyme having strand displacing polymerase activity and an enzyme having 5' double stranded specific exonuclease activity. It is believed that the independent claims 1 and 20, and claims 2-18 and 21-24 which depend from claim 1, are patentable.

In addition, new claims 25 and 26 have been added to depend from claims 1 and 20, respectively. The newly added claims recite that the enzyme having the strand displacing polymerase activity can also be the same enzyme that provides the 5' double stranded specific exonuclease activity. Consequently, the method covered by either claim 25 or claim 26 only requires one enzyme that can exhibit both strand displacing polymerize activity and 5' double stranded specific exonuclease activity. Since the new claims 25 and 26 include the subject matter deleted from claims 1 and 20, support for these claims can be found in the original claims, 1 and 20, and in the application on page 5, lines 8-11.

Independent claims 1 and 20 also were rejected under §112 for reciting the phrase "capable of hybridizing". These claims have been amended as suggested in the Office Action to refer to first and second primers which hybridize. (Office Action, page 3.) In addition, claims 22 and 23 were similarly amended. It is believed that independent claim 1 and claims 2-18 and

21-24 which depend from claim 1 and independent claim 20 are patentable. Withdrawal of all rejections under §112 for the pending claims is requested.

Rejections under 35 USC §103

Claims 1-6, 7-11, 13-18, and 20-24 were rejected under 35 USC §103(a) over Walker et al. (EP 0 500 224, "the '224 patent") in view of Walker et al. (US 5,470,723, "the '723 patent").

The Examiner's rejections are respectfully traversed. It is believed that the cited references do not disclose or make obvious the claimed invention. The present invention as covered by the claims utilizes first and second primers which incorporate a "digestion resistant region" remote from their 5' ends. There are additional primers referred to as the "third and fourth" primers each which have a degree of sequence homology with the partially digestible regions of the first and second primers respectively. The reaction also includes an enzyme system that provides both strand displacing polymerase activity and 5' double stranded specific exonuclease activity.

Referring now to Fig. 3 of the present application, it can be observed that the long primers A-B and C-D hybridize to single, complementary strands (Fig. 3d). The hybridized long primers A-B and C-D are extended by the enzyme having polymerase activity to provide double stranded molecules. The enzyme exhibiting 5' exonuclease activity then affects digestion starting from the 5' end of the respective strands. However, digestion cannot proceed further than the digestion resistant region. This leaves exposed regions that are complementary to the digestion regions. Since the third and fourth primers have a sequence homology with the digestible regions of the first and second primers, the short third and fourth primers hybridize at the exposed regions. The enzyme having strand displacing polymerase activity extends the chain from the short primers and, in doing so, displaces previously synthesized strands as outlined in step h of Fig. 3. Distinguishing features of the presently claims process include use of modified primers *i.e.,* the first and second primers that have a digestion resistant region and third and fourth primers, which have a sequence homology with the digestible regions of the first and second primers.

In the present application progressing from Figs. 3 h to 3 i, it can be seen that the enzyme having strand displacing activity displaces strands on the complementary target sequences. The displaced strands have the short third or fourth primers still attached and a portion of the complementary 3' binding region for the long, first or second primers. The "target strands" have

the 3' binding regions for the longer, first and second primers. All four strands, *i.e.*, the displaced strands and the "target strands", can now serve as templates for further amplification. (See Figs. 3j-3l.) (In practice, the method provides two of each double strand sequence illustrated in Fig. 3j.) This provides an exponential amplification of the original target strands. The process then repeats, beginning at Fig. 3m.

As noted by the Examiner, Walker (the '224 patent) discloses the use of only two primers. The '224 patent uses modified deoxynucleoside triphosphates to inhibit the exonuclease digestion of the double strand. In the present invention, it is the long primers that incorporate the digestion resistant region and which in conjunction with the third and fourth primers that have a degree of sequence homology provide exponential amplification of the target sequences.

The '723 patent does not make up for the deficiencies of the '224. The '723 patent also does not disclose or describe the use of a third and fourth primer that has sequence homology with at least a portion of the long primers that incorporate the digestion resistant region. Consequently, it is believed that these references either singly or in combination do not disclose or make obvious the claimed invention which uses both a set of long primers, each of which include a digestion resistant region, a set of short primers which have a degree of sequence homology with the partially digestible regions of the long primers, and which uses an enzyme having 5' double stranded exonuclease activity.

Furthermore, it is maintained that the modification as suggested by the Examiner would render the teaching of the '224 patent unsatisfactory for its intended purpose or to function as intended. The only thing that the '723 patent adds is multiple primer sequences. As noted above the '723 patent does not disclose additional primers that have the same function in the amplification process as that provided by the third and fourth primer of the present application. Further, adding an amplification primer, an adapter primer, or a bumper primer as described in the '723 patent to the reaction mixture described in the '224 patent would hinder amplification of the target primer.

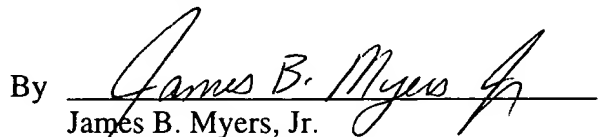
The '723 patent uses a strand displacement amplification. This method utilizes an amplification primer to hybridize to the 3' end of a target sequence. The amplification primer provides a recognition site for a nicking restriction enzyme at its 5' end. The amplification primer first binds directly to the target strand. The bumper primer then hybridizes upstream of the amplification primer and the polymerase extends the strand. The extended strand is then

displaced. The adapter primer hybridizes to the displaced extension product, which is itself extended and displaced to give a product containing the original second strand target sequence flanked on either side, one side with an amplification primer having a recognition site for a nicking restriction enzyme at its 5' end and an adapter primer having a sequence at its 3' end. This modified fragment then enters conventional SDA amplification by binding an extension of the amplification primer specific for the opposite target. Adding any of these primers to the '244 process followed by extension and displacement would serve to generate an unrelated template, which would ultimately reduce the amplification rate.

Neither the '224 patent nor '723 patent disclose or use processes having a first primer with a digestion resistant region, a short primer having a sequence homology with a digestible region of a longer primer, and a enzyme exhibiting exonuclease activity as presently claimed. Further more, incorporating one of the primers from the '723 patent into the process described in the '244 would significantly reduce or destroy amplification method described in the '244 patent. It is respectfully suggested that the claimed invention as claimed in independent claim 1 and independent claim 20 is not made obvious considering either the '224 or the '723 applications either singly or in combination. Consequently, withdrawal of the rejections over these references is requested.

Applicants respectfully submit that the pending claims are patentable. Accordingly, reconsideration leading to withdrawal of all the rejections under 35 USC §103 and §112 and allowance of this application containing claims 1-18 and 20-26 are respectfully requested. Additionally, the Examiner is invited to telephone the undersigned attorney if there are any questions about this submission or other formal matters, which may be addressed in that fashion.

Respectfully submitted,

By 

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